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ARTICLE

Guiding model-driven combination dose selection using multi-objective synergy optimization

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Abstract

Despite the growing appreciation that the future of cancer treatment lies in combination therapies, finding the right drugs to combine and the optimal way to combine them remains a nontrivial task. Herein, we introduce the Multi-Objective Optimization of Combination Synergy – Dose Selection (MOOCS-DS) method for using drug synergy as a tool for guiding dose selection for a combination of preselected compounds. This method decouples synergy of potency (SoP) and synergy of efficacy (SoE) and identifies Pareto optimal solutions in a multi-objective synergy space. Using a toy combination therapy model, we explore properties of the MOOCS-DS algorithm, including how optimal dose selection can be influenced by the metric used to define SoP and SoE. We also demonstrate the potential of our approach to guide dose and schedule selection using a model fit to preclinical data of the combination of the PD-1 checkpoint inhibitor pembrolizumab and the anti-angiogenic drug bevacizumab on two lung cancer cell lines. The identification of optimally synergistic combination doses has the potential to inform preclinical experimental design and improve the success rates of combination therapies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The biomedical community has long sought to identify synergistic drugs for which the combined effect is greater than additive. However, lack of consensus on the definition of additivity has complicated this goal, particularly because a combination classified as synergistic by one definition can be classified as antagonistic by another.

WHAT QUESTION DID THIS STUDY ADDRESS?

Here, we introduce the Multi-Objective Optimization of Combination Synergy – Dose Selection (MOOCS-DS) method as a rigorous approach to bring clarity and consistency to selecting an optimally synergistic dose for a preselected drug combination.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

MOOCS-DS bridges the gap between efficacy- and potency-based additivity definitions by identifying the set of possible combination doses and schedules for which one synergy metric cannot be improved without compromising the other.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This versatile methodology can become an invaluable tool for guiding optimally synergistic dose and schedule selection, supporting go/no-go criteria, and improving indication selection.

INTRODUCTION

The Food and Drug Administration's "Project Optimus" initiative challenges drug companies to improve combination therapy design, with a focus on how to get the right therapeutics, to the right patient, at the right dose.[1,2] There are two related, yet distinct, tasks in this initiative. The first is the question how to optimize the selection of combination partners for a specific disease, which is typically addressed using analyses of high throughput drug screens.[3,4] The second question, and the focus of this work, is how to optimize the dose and schedule of preselected drugs used in combination therapy. Even preclinically, where significantly more flexibility exists in testing different combination doses and schedules, designing an optimal protocol can be an intractable combinatorial problem. This may result in dismissing a promising combination because the more optimal doses were simply not tested.

One long sought-after goal of combination therapies is to identify compounds that act synergistically to achieve a desired outcome.[5] Synergy occurs when the combined effect is greater than what is expected in the additive case, whereas antagonism occurs when the combined effect is less than that expected from additivity.[6–9] Although this initially seems straightforward, the definition of additivity (or no interaction) has been "at the center of controversy among leading researchers of the topic for the last century."[6] The challenge that is familiar to all who have worked with synergy metrics is that additive does not mean "adding effects." A trivial but illustrative example is as follows: if drug A kills 60% of cancer cells at its saturating dose and drug B kills 50% at its saturating dose, the projected additive effect will not result in 110% of killed cells. The lack of a consensus definition of additivity confounds the search for synergistic combinations – we cannot find combinations whose efficacy is greater than additive if we do not have an agreed-upon definition of additivity.

An overwhelming number of quantitative definitions for drug additivity, with differing underlying assumptions, have been proposed over the last century. Many of these definitions fall into one of two categories: effect-based and dose-effect based approaches. Within the effect-based framework, drugs are synergistic if the efficacy (the output) of the combination dose exceeds the expected efficacy if the drugs had acted independently (Figure 1a) – this can be thought of as "synergy of efficacy" (SoE).[4] Within the dose-effect based framework, maximizing combination synergy is equivalent to identifying the smallest possible drug dose (the input) that achieves a target efficacy – this can be thought of as "synergy of potency" (SoP).[4,10,11] Table S1 briefly summarizes the classically used additivity metrics, and Table S2 introduces more recently proposed metrics. Excellent summaries can also be found elsewhere.[3,4,8,10,11]

The "fragmented state"[4] of the synergy quantification landscape has significant practical implications. In a recent meta-analysis,[3] it was shown that the "majority of assigned synergistic and antagonistic labels were ... unique to a certain metric." Of the existing synergy quantification approaches, the recently developed Multi-dimensional Synergy of Combinations (MuSyC) framework stands out as an approach that unifies the principles of effect-based and dose-effect based additivity.[4,12,13] MuSyC fits a generalized, multidimensional Hill equation to the dose–response surface for a combination therapy. SoP and SoE are captured through distinct parameters in this Hill equation. Unlike traditional frameworks, this assigns a combination therapy two synergy scores, allowing for a clear indication of whether the combination reduces toxicity (SoP), improves efficacy (SoE), or both/neither. This two-parameter synergy score can be used to make informed decisions about not only what drugs are most synergistic, but the nature of the combination's synergy.

The work presented here aims to decouple and assess SoE and SoP in a similar spirit to the MuSyC framework. However, whereas MuSyC aims to improve the process of drug selection by identifying the most synergistic drug combinations from high throughput screening, we seek to improve the process of dose optimization and scheduling for two preselected drugs. We propose to do this by solving

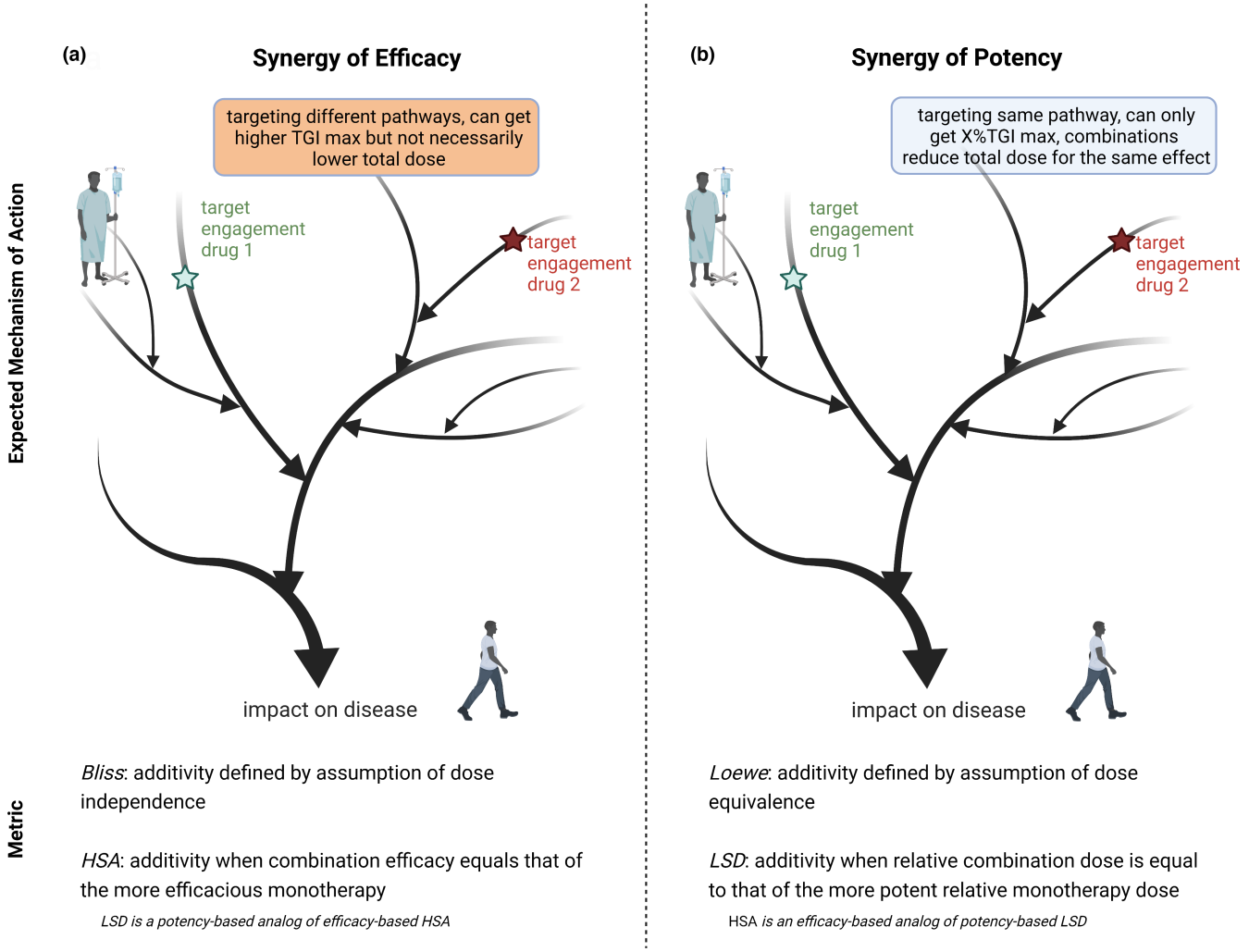


FIGURE 1 Schematic diagram of two main ways to define combination synergy, namely, (a) synergy of efficacy (output) and (b) synergy of potency (input). The metrics used throughout the paper are indicated in its corresponding category. HSA, highest single agent; LSD, lowest single dose; TGI, tumor growth inhibition.

a multi-objective optimization problem across dosing space, with the two objectives being SoP and SoE.

The paper is organized as follows. In the Methods section, we give an overview of the commonly used effect-based and dose-effect based additivity frameworks, and we define a new dose-effect based metric. We also introduce a multi-objective optimization formulation of the SoE and SoP quantification problem – we call this the Multi-Objective Optimization of Combination Synergy – Dose Selection (MOOCS-DS), with an intentional tribute being paid to the similarly named MuSyC method. This multi-objective formulation is applied to two cases: a deliberately simplified toy model, and a real-world model of the combination of the PD-1 checkpoint inhibitor pembrolizumab (brand name Keytruda) and the anti-angiogenic drug bevacizumab (brand name Avastin). These models are introduced in the Methods section, and the results of applying the MOOCS-DS framework to these models are found in the Results section. In the Discussion, we give concluding thoughts on how this methodology can help guide preclinical experimental design, as well as the translational challenges that remain for its applicability in the clinic.

METHODS

Throughout the paper, we use the following notational conventions. D_i is a monotherapy dose, d_i is the dose of drug i used in a combination, the effect/response E_i describes the tumor growth inhibition (TGI) induced by the dose under consideration relative to the control, that is: $\text{TGI} = E_i = X_{\text{dose}}(t_f)/X_{\text{control}}(t_f)$, where $X_{\text{dose}}(t_f)$ is the tumor size at the terminal timepoint t_f in response to the specified treatment protocol, and $X_{\text{control}}(t_f)$ is the tumor size at this terminal timepoint in the absence of drug. By definition, $0 \leq E_i \leq 1$.

Overview of classic synergy quantification metrics

The effect-based metric of Bliss additivity is named after C.I. Bliss who developed it in 1939.[14] Bliss assumed that the drugs do not interact with each other, and that the drugs elicit their responses independently, yet contribute to a common effect,[7,10] as illustrated in Figure 1a. This results in the following expected additive (no interaction) response to combination therapy of dose d_1 of drug 1 and d_2 of drug 2:

$$E_{\text{Bliss}}(d_1,d_2) = E(d_1,0) + E(0,d_2) - E(d_1,0)E(0,d_2). \tag{1}$$

If the actual response of the combination therapy satisfies $E(d_1,d_2) > E_{\text{Bliss}}(d_1,d_2)$, then the combination dose is classified as synergistic. If the actual efficacy of the combination satisfies $E(d_1,d_2) < E_{\text{Bliss}}(d_1,d_2)$, then it is classified as antagonistic.

Following the standard in the literature, the Bliss combination index (CI)[15,16] is defined as the ratio of the expected additive efficacy to the actual efficacy:

$$\text{CI}_{\text{Bliss}}(d_1,d_2) = \frac{E_{\text{Bliss}}(d_1,d_2)}{E(d_1,d_2)}. \tag{2}$$

Using this metric, when CI equals one, the combination is classified as additive, when CI is less than one, it is synergistic, and when CI is greater than one, it is antagonistic. The strengths and weaknesses of Bliss additivity have been explored in detail elsewhere[3,10] and are briefly summarized in Table S1.

The highest single agent (HSA) framework is another effect-based approach. It classifies a combination as additive if its efficacy equals to that of the more efficacious monotherapy[3]:

$$E_{\text{HSA}}(d_1,d_2) = \max\{E(d_1,0), E(0,d_2)\}. \tag{3}$$

If the actual response to the combination therapy satisfies $E(d_1,d_2) > E_{\text{HSA}}(d_1,d_2)$, the combination dose is classified as synergistic. If instead $E(d_1,d_2) < E_{\text{HSA}}(d_1,d_2)$, the combination is classified as antagonistic. This results in an HSA CI of:

$$\text{CI}_{\text{HSA}}(d_1,d_2) = \frac{E_{\text{HSA}}(d_1,d_2)}{E(d_1,d_2)}, \tag{4}$$

where again CI equals one indicates additivity, CI less than one indicates synergy, and CI greater than one indicates antagonism. As described in Figure S1 and Table S1, HSA generally imposes a lower bar for synergy (of efficacy) than Bliss.

Loewe additivity, named after S. Loewe, who developed it in 1926 with H. Muiscaniek,[17] is a dose-effect approach applicable when two drugs have similar modes of action on the same pathway (Figure 1b). Loewe assumed that for any monotherapy dose D_1 of drug 1, there exists a monotherapy dose D_2 of drug 2 with the same efficacy ($E(D_1,0) = E(0,D_2)$). That is, Loewe assumed that the drugs are interchangeable, and that the effect of one can be achieved through scaling the dose of the other – this is referred to as the Dose Equivalence Principle.[3,18]

Consider only combination doses (d_1,d_2) that achieve the same effect E as monotherapies:

$$E(d_1,d_2) = E(D_1,0) = E(0,D_2). \tag{5}$$

As derived in Figure S2, Loewe's definition of additivity is:

$$\frac{d_1}{D_1} + \frac{d_2}{D_2} = 1 \tag{6}$$

For a fixed efficacy, this defines a line called an isobole (iso = equal and bolus = dose) through $d_1 - d_2$ dosing space for which a combination is classified as additive.[18] Alternative approaches to computing and analyzing isoboles that are not limited by the Dose Equivalence Principle have also been considered.[17,19]

If the actual combination dose (d_1,d_2) that achieves the efficacy of the monotherapy is smaller than that predicted by Loewe, the combination is deemed synergistic. If it is larger, the combination is deemed antagonistic. This leads to the following definition of the Loewe CI:

$$\text{CI}_{\text{Loewe}}(d_1,d_2) = \frac{d_1}{D_1} + \frac{d_2}{D_2} = \begin{cases} = 1, \text{ additive} \\ < 1, \text{synergy} \\ > 1, \text{ antagonism} \end{cases}$$

Table S1 explores strengths and limitations of Loewe's definition of additivity. Beyond these three classic metrics, a number of other additivity metrics have been proposed in the last few decades. We highlight these in Table S2, while also noting that excellent reviews of existing additivity metrics can be found elsewhere.[3,4,10,11]

A novel dose-effect based additivity framework

Here, we introduce an additional dose-effect based additivity framework that can be viewed as a potency-based equivalent to the efficacy-based HSA metric (Figure 1). HSA classifies a combination as additive if its efficacy is equal to that of the most effective monotherapy. We

propose a complementary lowest single dose (LSD) CI, which defines a combination as additive if its relative combination dose is equal to that of more potent relative monotherapy dose.

To define a relative dose, we will use a quantity we call the percent inhibition (PI_{50}) value. We define this as the dose of drug i that results in 50% TGI relative to control (i.e., $E(PI_{50}^1, 0) = E(0, PI_{50}^2) = 0.5$). The relative potency of drug i at monotherapy dose D_i is then defined as the ratio of the dose to its PI_{50}^i value: D_i / PI_{50}^i. This can be thought of as dose normalization, which allows the potency of different drugs to be compared. Now consider two drugs with the same efficacy (i.e., $E(D_1, 0) = E(0, D_2)$). We can compare their potency using the values of D_1 / PI_{50}^1 and D_2 / PI_{50}^2. In the LSD framework, a combination (d_1, d_2) that achieves the same efficacy as the monotherapy (i.e., $E(D_1, 0) = E(0, D_2) = E(d_1, d_2)$) is additive if the relative combination dose, as follows:

$$d_{combo}(d_1, d_2) = \frac{d_1}{PI_{50}^1} + \frac{d_2}{PI_{50}^2} \tag{7}$$

is equal that of the more potent monotherapy:

$$D_{pot}(D_1, D_2) = \min\left\{\frac{D_1}{PI_{50}^1}, \frac{D_2}{PI_{50}^2}\right\}. \tag{8}$$

Note that we take the minimum value of the relative potencies, because it is the drug that achieves the same efficacy at the lower relative dose that is more potent. Thus, if the relative combination dose $d_{combo}(d_1, d_2)$ is lower than the additive expectation defined in D_{pot}, then the combination is classified as synergistic. Otherwise, it is classified as antagonistic. This leads to a CI of:

$$CI_{LSD}(d_1, d_2) = \frac{d_{combo}(d_1, d_2)}{D_{pot}(D_1, D_2)}, \tag{9}$$

which is consistent with prior definitions that classify CI less than one as synergy and CI greater than one as antagonism.

As an example, suppose that drug 1 has a $PI_{50}^1 = 20$ (dose of 20 gives 50% TGI relative to control) and that drug 2 has $PI_{50}^2 = 2$. Further suppose that $E(25, 0) = E(0, 3) = E(12, 1)$, meaning the TGI relative to the control are equivalent whether we give: drug 1 as monotherapy at dose $D_1 = 25$, drug 2 as monotherapy at dose $D_2 = 3$, and the combination with drug 1 given at dose $d_1 = 12$ and drug 2 given at dose $d_2 = 1$. Because the ratio $D_1 / PI_{50}^1 = 25/20 = 1.25$ whereas $D_2 / PI_{50}^2 = 3/2 = 1.5$, drug 1 is more potent as we must give a smaller relative amount of drug 1 than drug 2 to achieve the same TGI. By equation 8, $D_{pot}(D_1, D_2) = 1.25$. Because the combination with $d_1 = 12, d_2 = 1$ has the same TGI as these monotherapies, we get $d_{combo}(d_1, d_2) = 12/20 + 1/2 = 1.1$. Thus, the relative combination dose that achieves the specified TGI is smaller than the more potent relative monotherapy. This results in a CI_{LSD} value of 1.1/1.25 which is less than 1, classifying the combination as synergistic.

Multi-objective optimization

The debate over whether synergy should be defined in terms of potency or efficacy has raged for nearly a century. However, as has been recently observed, "the search for a reference analysis framework will not find its solution in one ideal model but rather in using a set of appropriate methods."[10] In that spirit, and in the spirit of the MuSyC method[4,12,13] which identifies both a SoP and SoE parameter for a combination (as compared to a dose-specific score), we propose the use of multi-objective optimization in dosing space to approach the synergy quantification problem. We call our method MOOCS-DS for Multi-Objective Optimization of Combination Synergy-Dose Selection.

Multi-objective problems have multiple objectives (f_i) to be optimized simultaneously over the set of feasible decision vectors $X \subseteq R^n$. Generally, the objectives in such an optimization problem compete with one another (i.e., a decision vector that optimizes one objective does not optimize the other). To address this, we will use the notion of Pareto optimality[20] to solve a multi-objective optimization problem that seeks to maximize SoP and SoE. Given that for all metrics synergy is maximized at lower CI values, this goal is equivalent to minimizing the corresponding CI value.

In the context of two objective functions, Pareto optimal solutions are the set of all decision vectors for which one objective cannot be improved without a second objective worsening.[20] Such decision vectors are referred to as non-inferior solutions. Finding a Pareto optimal solution set requires mapping points from the design space to the criterion (objective) space.[20] In the context of maximizing SoP and SoE over a range of drug doses, design space is the space of feasible drug doses, and criterion space is the space of SoP and SoE CI values. The Pareto optimal set (called the Pareto front) is the set of drug doses for which one synergy measure cannot be improved without the other synergy measure worsening. Each solution on the Pareto front corresponds to a point in design space, meaning a dose of each drug.

Toy model for exploration of synergy metrics

We first use a toy model to better understand how the output of the MOOCS-DS method depends on the choice

of synergy metrics. The toy model describes a logistically growing tumor $x(t)$ treated with two "drugs." The effects of drug 1 are captured in the linear kill term with a killing rate of d_1, and the effects of drug 2 are captured in the quadratic kill term with a killing rate of d_2:

$$\frac{dx}{dt} = 0.2x\left(1 - \frac{x}{10}\right) - d_1 x - d_2 x^2,\ x(0) = 1. \tag{10}$$

Note we are using the notation d_1 and d_2 for the rate terms as they can be thought of as the toy model's proxy for a drug dose. Across "dosing" space, SoE will be assessed using the CIs for Bliss and HSA and SoP will be assessed using the CI for Loewe and LSD. This will allow us to directly compare synergy and antagonism classifications and the Pareto optimal doses that solve the multi-objective optimization problem without delving into the complexity of mechanistic or semimechanistic models of drug distribution and action.

Pembrolizumab and bevacizumab model

We also consider an example involving two existing anticancer drugs, a PD-1 checkpoint inhibitor pembrolizumab, and an anti-angiogenic agent bevacizumab. Qiao et al.[21] reported that this combination inhibited tumor growth compared to monotherapy without overt toxicity in two mouse models of human non-small cell lung cancer (NSCLC), the p53 wild-type A549 cells and the p53-deficient H1299 cells. The animals received either: (1) 10 mg/kg of pembrolizumab starting on day 3, then given every three days (Q3D) until five doses have been administered, (2) 1 mg/kg of bevacizumab starting on day 0, then given every three days until six doses have been administered, or (3) a combination of these two drugs using the same protocol. The question we explore here is whether the selected dose and schedule is optimally synergistic, or if our proposed methodology can identify a more synergistic protocol.

To address this, we propose a standard pharmacokinetic-TGI (PK-TGI) model for both drugs given as monotherapy or in combination. Drug PKs were parametrized separately using literature data, with bevacizumab best described by a one-compartment PK model parameterized using data from Lin et al.,[22] and pembrolizumab best described by a two-compartment PK model parametrized with data from Lindauer et al.[23] For both models, it is assumed that the drug is administered intravenously into the central (plasma) compartment at a rate k_{01} and that the drug can be cleared from the plasma compartment at a rate k_{10}. Pembrolizumab can also distribute into the peripheral compartment at a rate k_{12} and return into the central compartment at a rate k_{21}. Finally, it is assumed that the tumor grows logistically, and can be killed as a function of concentration of either of the drugs. This results in the following system of equations, whose structure is summarized in Figure 2a–c.

$$\left.\begin{aligned} \frac{dD1_{dose}}{dt} &= -k_{01p} D1_{dose} \\ \frac{dD1_p}{dt} &= k_{01p} D1_{dose} - k_{10p} D1_p - k_{12p} D1_p + k_{21p} \frac{V_{2p}}{V_{1p}} D1_T \\ \frac{dD1_T}{dt} &= k_{12p} \frac{V_{1p}}{V_{2p}} D_{1P} - k_{21p} D1_T \end{aligned}\right\} \text{pembrolizumab}$$

$$\left.\begin{aligned} \frac{dD2_{dose}}{dt} &= -k_{01b} D2_{dose} \\ \frac{dD2_p}{dt} &= k_{01b} D2_{dose} - k_{10b} D2_p \end{aligned}\right\} \text{bevaciazumab}$$

$$\left.\begin{aligned} \frac{dx_1}{dt} &= r x_1\left(1 - \frac{X}{K}\right) - x_1\left(k_{2p} D_{1p} + k_{2b} D2_p + k_3 D1_p D2_p\right) \\ \frac{dx_2}{dt} &= x_1\left(k_{2p} D_{1p} + k_{2b} D2_p + k_3 D1_p D2_p\right) - k_1 x_2 \\ \frac{dx_3}{dt} &= k_1\left(x_2 - x_3\right) \\ \frac{dx_4}{dt} &= k_1\left(x_3 - x_4\right) \\ X &= x_1 + x_2 + x_3 + x_4 \end{aligned}\right\} \text{tumor} \tag{11}$$

The model is parameterized as described in Table 1. With the exceptions of the doses and initial tumor size, the initial value of each variable is identically zero. $D1_{dose}$ and $D2_{dose}$ are determined by the dose of pembrolizumab and bevacizumab administered, respectively. The initial tumor size for the H1299 cell line is $x_1(0) = 36.865$ and for the A549 cell line is $x_1(0) = 43.626$. The fits to the experimental datasets[21] are shown in Figure 2d–k.

RESULTS

The MOOCS-DS algorithm, available at https://github.com/jgevertz/MOOCS-DS, is implemented in MATLAB using ode45 as the numerical differential equation solver. The code is modularized so that with minimal work, a user can insert their own model of combination therapy and the Pareto optimization step of MOOCS-DS is automated. In particular, the user would only have to redefine the *combinations_TGI* function to encode their differential equation model, and the function *set_parameters_ICs_protocol* to define the parameters, initial conditions, and dosing protocol.

Toy model

First, we numerically find monotherapy "doses" (values of d_1 and d_2) in the toy model that achieve tumor growth inhibition from 5% (PI_5) to 85% (PI_{85}) relative to control;

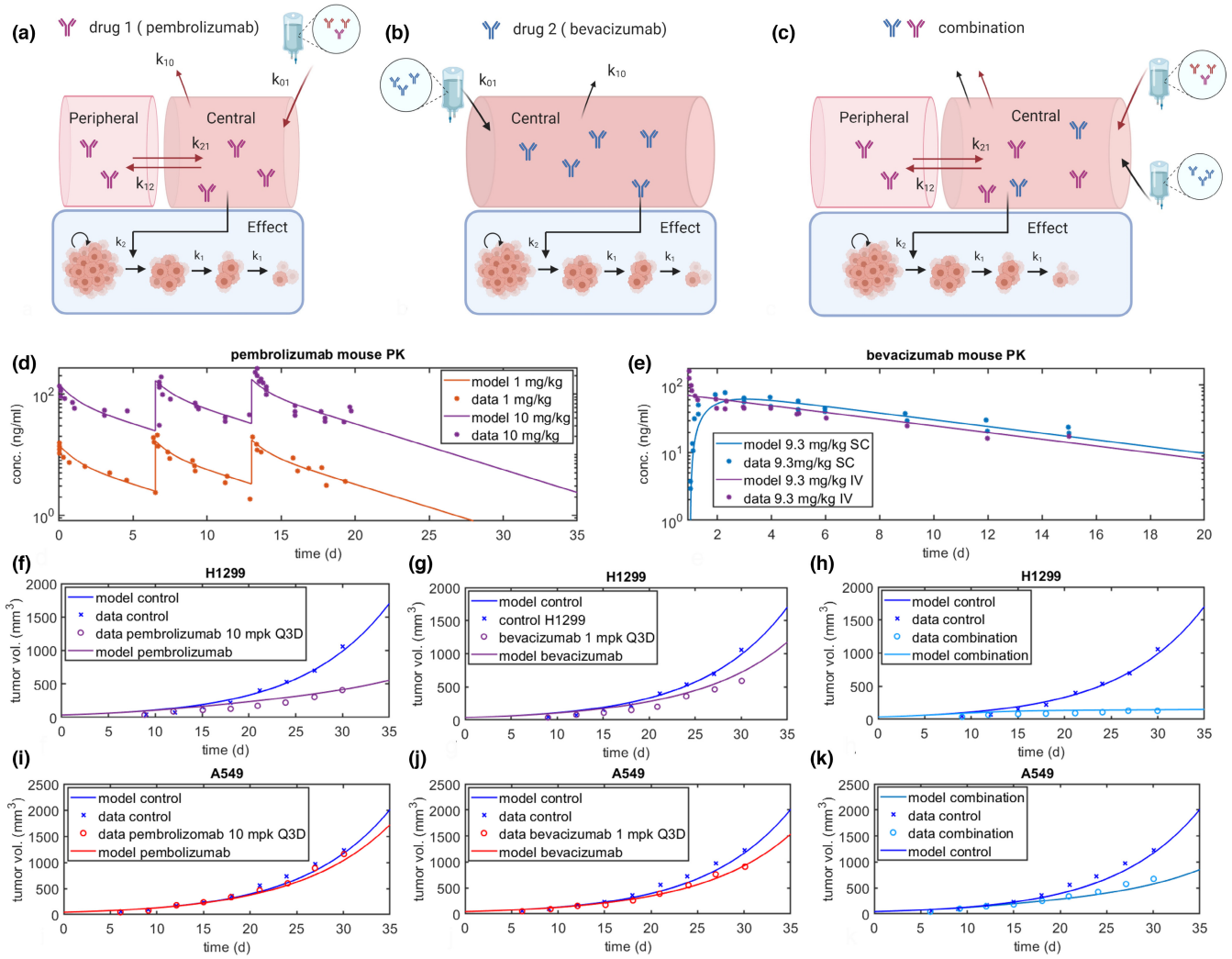


FIGURE 2 (a–c) Schematic model structure for System 11 describing the impact of (a) pembrolizumab as monotherapy, (b) bevacizumab as monotherapy, and (c) combination therapy of pembrolizumab and bevacizumab on tumor volume reduction. Fits for components of System 11. Second row: Mouse PK data for (d) pembrolizumab (digitized from ref. 23) and (e) bevacizumab (digitized from ref. 22). Third row: Fits for H1299. Fourth row: fits for A549. (f) and (i) show fits to control data and treatment TGI using 10 mg/kg of pembrolizumab as specified in ref. 21. (g) and (j) show fits to control data and treatment TGI using 1 mg/kg of bevacizumab as specified in ref. 21. (h) and (k) show fits to control data and combination TGI using 10 mg/kg of pembrolizumab and 1 mg/kg of bevacizumab as specified in ref. 21. PK, pharmacokinetic; TGI, tumor growth inhibition.

the TGI range was chosen arbitrarily to showcase the method's application. We then compute the various combination indices at the dimensionless time point of $t_f = 10$ (Figure 3a–d).

From the point of view of SoE, Bliss predicts that all combinations range from additive to slightly antagonistic, with a maximum CI of 1.065. On the other hand, HSA predicts that all combinations range from additive to synergistic, with a minimum CI of 0.519. Notably, not only do the combination dose classifications differ across CI metrics, but the very structure of the CI function in dosing space differs. Doses that HSA identifies as being near-optimally synergistic (blue in Figure 3b) fall in the region of near-maximal antagonism according to Bliss (yellow in Figure 3a). Similar structural discrepancies are found if the two SoP measures are compared (Figure 3c,d). This highlights how the SoE or SoP metrics utilized can greatly influence synergistic dose selection, even in a simplistic toy model.

Due to these inconsistent predictions, it is expected that the doses that solve the multi-objective synergy optimization problem will sensitively depend on how we define SoP and SoE. To test this hypothesis, we applied the MOOCS-DS method in four criterion spaces: Loewe-Bliss, Loewe-HSA, LSD-Bliss, and LSD-HSA. The resulting Pareto fronts are shown in Figure S3 and the Pareto optimal doses are shown in Figures S4 and 3e. In Figure 3e, we see that no combination dose is found on

TABLE 1 Parameters used in System 11 to describe data in Figure 2d–k.

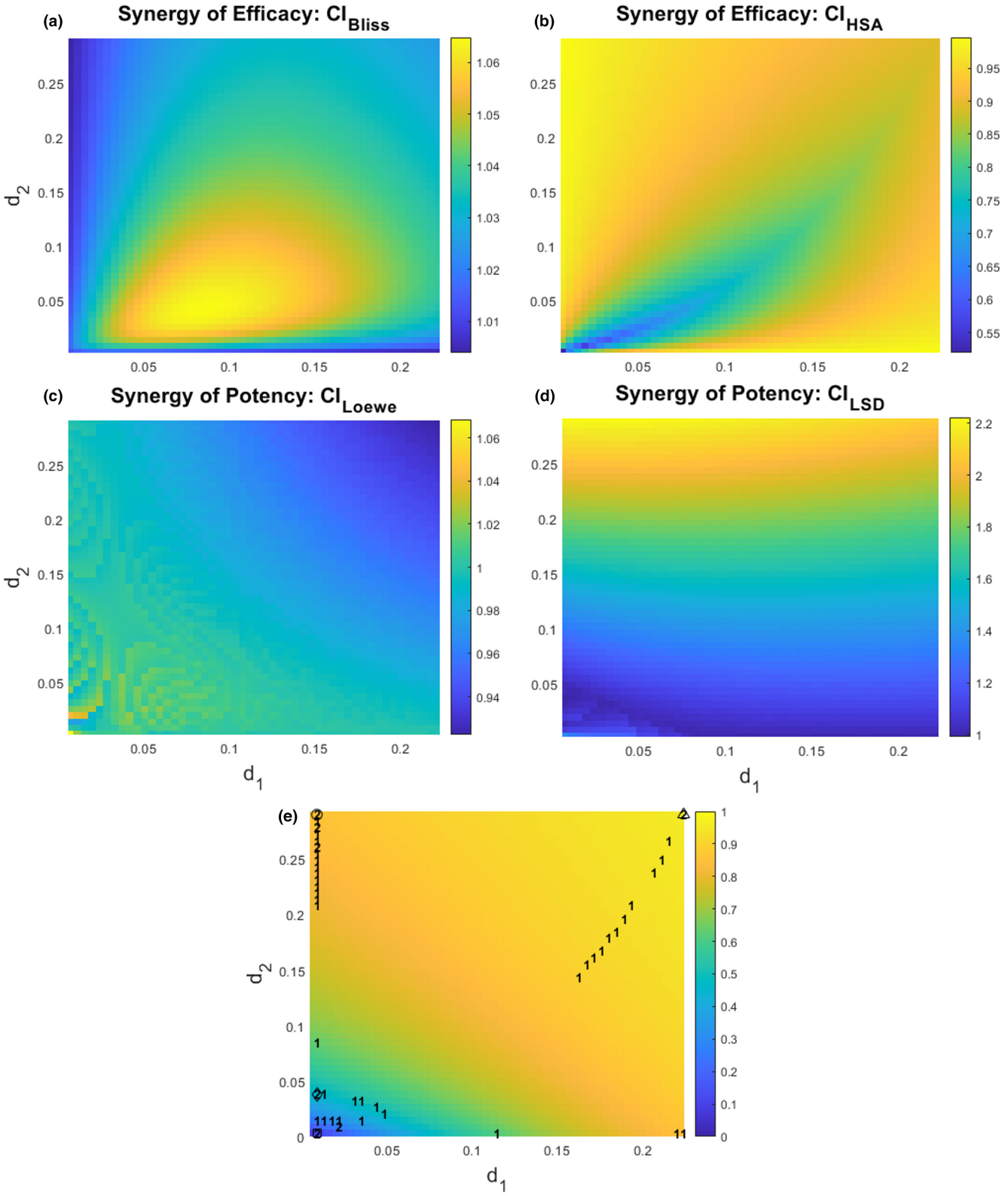
Parameter	Description	Value		Units	Refs.
Pembrolizumab					
V_{1p}	Volume of distribution, central compartment	70		mL/kg	Calibrated to data in ref. 23
V_{2p}	Volume of distribution, peripheral compartment	33		mL/kg	
Cl_{1p}	Clearance, central compartment	20		mL/kg/day	
Cl_{2p}	Clearance, peripheral compartment	22		mL/kg/day	
k_{10p}	Rate of drug clearance from the central compartment for drug	Cl_{1p}/V_{1p}		1/day	
k_{12p}	Rate constant for drug distribution from central to peripheral compartment	Cl_{2p}/V_{1p}		1/day	
k_{21p}	Rate constant for drug distribution from peripheral to central compartment	Cl_{2p}/V_{2p}		1/day	
k_{01p}	Drug absorption rate for subcutaneous (sc) administration	0.11		1/day	
Bevacizumab					
V_{1b}	Volume of distribution, central compartment	119		mL/kg	Calibrated to data in ref. 22
V_{2b}	Volume of distribution, peripheral compartment	13.6		mL/kg/day	
k_{10b}	Rate of drug clearance from the central compartment	Cl_{1b}/V_{2b}		1/day	
k_{01b}	Drug absorption rate for subcutaneous (sc) administration	1.3		1/day	
Tumor					
K	Tumor carrying capacity	10,000		mm^3	n/a
r	Intrinsic rate of tumor growth	0.11		1/day	Ref. 21
k_{2p}	Rate of tumor elimination by pembrolizumab as monotherapy	**H1299**	**A549**		
		0.0008	0.0001	1/day	Calibrated to data in ref. 21
k_{2b}	Rate of tumor elimination by bevacizumab as monotherapy	0.0011	0.0008	1/day	
k_3	Rate of tumor kill by combination of bevacizumab and pembrolizumab	0.0001	0.00002	1/day	
k_1	Kinetic cell death parameter	0.000575		1/day	

all four Pareto fronts, and that only a small number of doses appear on two Pareto fronts (indicated with a "2"). Most Pareto optimal doses are classified as optimally synergistic in only one of the four criterion spaces ("1" in Figure 3e). We also observe that the combination dose that maximizes any individual synergy metric always falls on the Pareto front in criterion spaces defined with that metric. As an example, the Bliss optimal solution (circle in Figure 3e) always falls on the Loewe-Bliss and the LSD-Bliss Pareto front.

In summary, the toy model demonstrates significant predictive discrepancies in synergy classification. Doses identified as synergistic by one metric can be classified as antagonistic by another, even within the same class of methods (that is, comparing across only SoE or SoP metrics). This confounds the problem of identifying optimally

FIGURE 3 (a)–(d) Combination indices (CIs) for toy model. Top row shows synergy of efficacy (SoE) CI values using (a) Bliss and (b) HSA. Note that the color bars are different – for Bliss the CI values range from 1.003 (essentially additive) to 1.065 (slight antagonism), whereas for HSA the CI values range from 0.519 (synergy) to 0.997 (essentially additive). Bottom row shows synergy of potency (SoP) CI values as computed using (c) Loewe and (d) LSD. The color bars are again different – for Loewe the CI values range from 0.922 (slight synergy) to 1.069 (slight antagonism), whereas for LSD the CI values range from 0.991 (slight synergy) to 2.219 (antagonism). (e) Number of criterion spaces (of the four considered) for which MOOCS-DS identifies a dose as Pareto optimal for the toy model in Equation 10. Figure S4 shows the breakdown of dose optimality by the definition of multi-synergy objective space. The color in the heatmap in (e) indicates the predicted TGI relative to the control for the combination dose. The synergistically optimal dose identified by each individual metric is also indicated using a circle for Bliss, square for HSA, triangle for Loewe, and diamond for LSD. HSA, highest single agent; LSD, lowest single dose; MOOCS-DS, Multi-Objective Optimization of Combination Synergy – Dose Selection; TGI, tumor growth inhibition.

synergistic doses, as the Pareto optimal doses sensitively depend on how SoE and SoP are defined. These inconsistent predictions on the toy model are in line with recent meta-analysis of oncology drugs where it was found that the "majority of assigned synergistic and antagonistic labels were ... unique to a certain metric."[3] We explore the consequences of these inconsistencies on the usability of MOOCS-DS in the Discussion.



Pembrolizumab and bevacizumab model

To study synergy in the model of pembrolizumab and bevacizumab, we choose a dosing range such that the maximal relative TGI for a combination is 95%, which corresponds to considering pembrolizumab and bevacizumab monotherapy over its PI_5 (5% TGI relative to control) to PI_{70} dosing range. For the less responsive p53-wild type A549 NSCLC cells in ref. 21, this corresponds to a model-predicted dosing range of 3.28 to 87.2 mg/kg for pembrolizumab and 0.19 to 4.76 mg/kg for bevacizumab. All synergy metrics are computed 5 days after the reported data collection window, which corresponds to day $t_f = 35$. Most of the results presented are for A549, although we also briefly summarize the results for the more responsive p53-deficient H1299 NSCLC cells.

Experimental schedule for A549

Here, we keep the schedule fixed at that used in ref. 21 and seek to find combination doses that solve the multi-objective SoE and SoP optimization problem. The CI heatmaps using the four synergy metrics are found in Figure S5. Interestingly, and in stark contrast to the toy model, within the same class of metrics we find much more consistency in synergy/antagonism classifications. Looking at the SoP metrics, we see that the structure of the CI function over the dosing space is independent of our use of Loewe or LSD (bottom row in Figure S5). Even the numerical values of the CI are quite similar. We do not see quite the same structural similarities across the SoE metrics (top row in Figure S5), although the regions of highest and lowest CI values do overlap significantly.

We applied the MOOCS-DS method in four different criterion spaces: Loewe-Bliss, Loewe-HSA, LSD-Bliss, and LSD-HSA. The resulting Pareto fronts are shown in Figure 4a. We observe that the Pareto fronts are smooth, unlike the jagged fronts found in the toy model. They also have a similar structure independent of how we quantify SoP and SoE, which is to be expected given the similar structure of the SoE and SoP CI functions (Figure S5).

In Figures 4b and S6, we explore if the similarity in the structure of the Pareto fronts corresponds to similar doses being identified as Pareto optimal. All Pareto optimal doses, and in fact all doses, have CI values less than one, indicating that all doses are classified as having synergistic potency and efficacy. Unlike in the toy model, here we find that the Pareto optimal doses are not highly sensitive to the choice of SoP and SoE metrics. Among doses identified as Pareto optimal in at least one criterion, just over 23% are classified as optimal in two or more criterion spaces ("2," "3," or "4," in Figure 4b) and just under 10% appear on the Pareto front in all four criterion spaces. Further, the doses that only fall on one Pareto front are very close to other doses that also fall on one Pareto front. As with the toy model, a dose that maximizes an individual synergy metric always falls on the Pareto front in criterion spaces defined with that metric. In this case, we also see that the optimally synergistic dose using only LSD is even on the Pareto front in the Loewe-HSA criterion space. Interestingly, out of the two SoP metrics, the LSD framework does not identify any combinations with a high dose of pembrolizumab (>38 mg/kg) as Pareto optimal, whereas Loewe can classify such combinations as optimally synergistic.

The combination dose used in the original experiment (red star in Figure 4b[21]) does not fall on any Pareto front. However, it served as a starting point for this analysis, and using the MOOCS-DS output, a research team can select the next dose or a set of doses to test experimentally. A team may look for a Pareto optimal dose that minimally changes their current dosing strategy: for A549 cell line, that would require increasing the dose of pembrolizumab by 49%, keeping the bevacizumab dose essentially fixed. However, this is not the only way to identify a dose for further study. Given the various ways to define the multi-objective synergy criterion space, another approach could be to select a dose that appears on all four Pareto fronts. For instance, Figure 4b indicates that the dose of 32.2 mg/kg of pembrolizumab and 1.77 mg/kg of bevacizumab is Pareto optimal for A549 according to all metrics. Although there are other doses that also fall on four Pareto fronts, this is the dose that also maximizes the TGI relative to the control (color in Figure 4b indicating 90.8% relative TGI). If achieving further TGI is desired, another reasonable choice among the Pareto optimal doses would be 35.1 mg/kg of pembrolizumab and 1.92 mg/kg of bevacizumab. This point falls on three Pareto fronts (all but Loewe-Bliss, see Figure S6) and corresponds to a projected 91.9% TGI relative to control. The feasibility of such adjustments must then be evaluated by the experimental team. Alternatively, if the doses that optimize synergy are prohibitively large, this analysis may serve as a part of a no-go criterion for pursuing this combination therapy for this disease.

We repeated the MOOCS-DS analysis for the more responsive p53-deficient H1299 NSCLC cells (see Figures S7, S8) and found that the Pareto optimal doses were again highly conserved across multi-objective synergy spaces. The combination dose in the original H1299 experiment is not Pareto optimal, although, in this case, the predicted minimum change in the experimental dose that makes it Pareto optimal requires slightly more than doubling the dose of bevacizumab (without having to increase the dose of pembrolizumab).

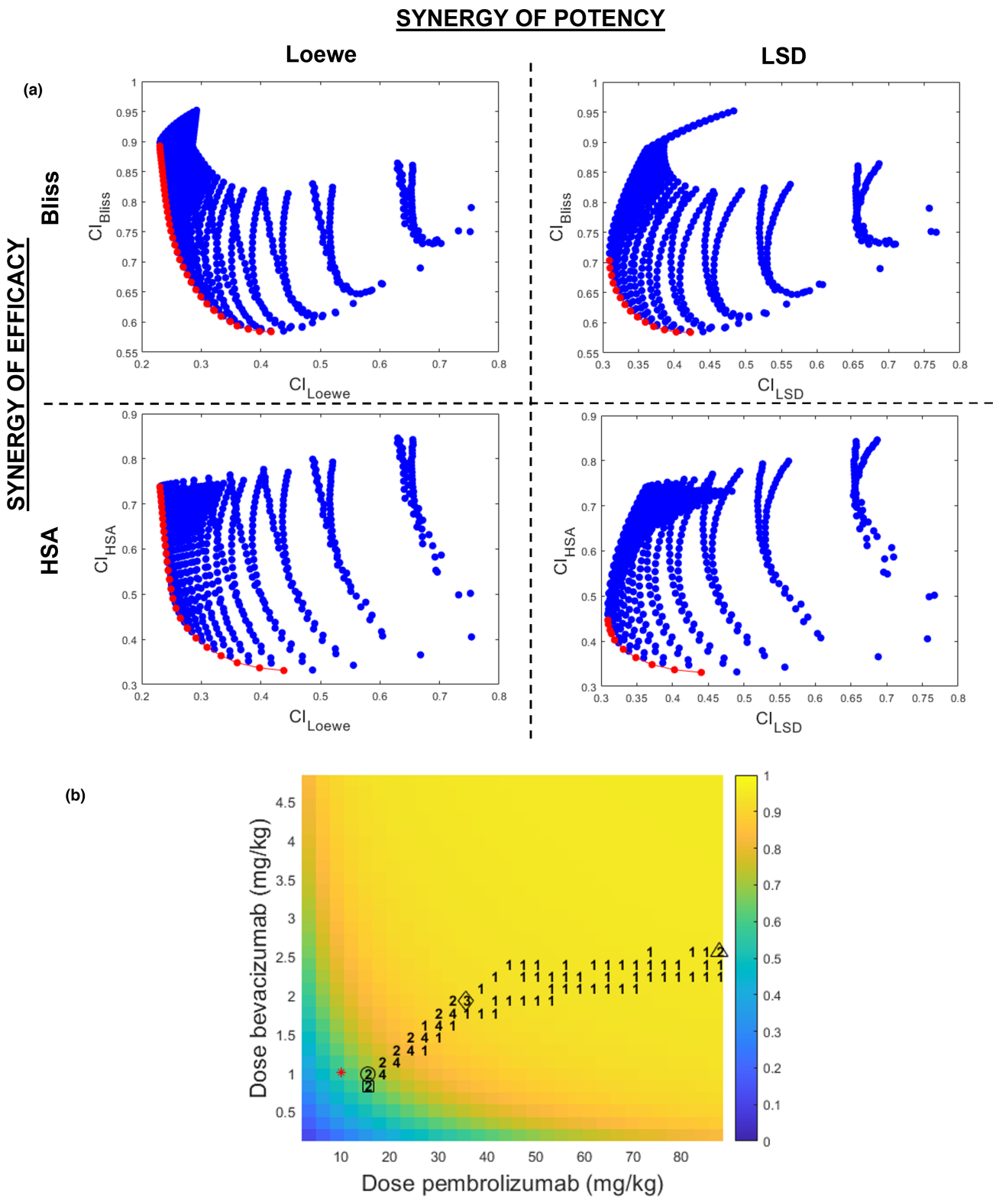


FIGURE 4 (a) Pareto fronts (indicated in red) for the pembrolizumab and bevacizumab model (A549 cell line) in four different criterion spaces. Top row: SoE defined by Bliss. Bottom row: SoE defined by HSA. Left column: SoP defined by Loewe. Right column: SoP defined by LSD. Blue points correspond to combination doses that are not Pareto optimal. (b) Number of criterion spaces (of the four considered) for which a dose is Pareto optimal for the pembrolizumab and bevacizumab model (A549 cell line). Figure S6 indicates the breakdown of dose optimality by the definition of multi-synergy objective space. The color in the heatmap indicates the predicted TGI relative to the control for the combination dose. The red star indicates the dose used in experiments.[21] The synergistically optimal dose identified by each individual metric is also indicated using a circle for Bliss, square for HSA, triangle for Loewe, and diamond for LSD. CI, combination index; HSA, highest single agent; LSD, lowest single dose; SoE, synergy of efficacy; SoP, synergy of potency; TGI, tumor growth inhibition.

In summary, independent of the cell line considered, the Pareto optimal doses identified by MOOCS-DS in the pembrolizumab and bevacizumab model are not highly sensitive to the metric used to define SoP and SoE. There are also no inconsistent classifications (i.e., all the doses in this case were consistently classified as additive or synergistic regardless of the metric). Performing the multi-objective optimization in four different criterion spaces and looking for doses that appear on multiple Pareto fronts provides one way to select a Pareto optimal dose for experimental validation. Considering the desired TGI at a fixed timepoint, or the likelihood of adverse events given the dosage required, can help to further narrow down the set of combination doses to consider.

Alternative dosing schedules for A549

The MOOCS-DS approach can also be used to study the impact of the timing of dose administration. In the original experimental protocol, both drugs were given Q3D, one starting on day 0 and the other on day 3. Here, we analyzed the impact of administering the five doses of pembrolizumab anywhere from daily (QD) to every fifth day (Q5D) and administering the six doses of bevacizumab anywhere from QD. to Q5D. This results in analyzing 25 different administration schedules. The day at which treatment is initiated is fixed as defined in the experimental protocol. This range of dose spacing still permits all doses to be administered the specified number of times over a 35-day window.

For each of the four multi-objective synergy spaces, MOOCS-DS produces a set of 25 plots in dosing space that indicate the Pareto optimal doses for each of the 25 schedules. Figure S9 shows six of the 25 plots produced when optimization is performed in the LSD-HSA criterion space. Using this definition of multi-objective synergy space, teams can identify both optimally synergistic schedules and doses. This is demonstrated in Figure 5a, which shows the Pareto front for all 25 considered protocols in LSD-HSA criterion space. Given that higher synergy corresponds to lower CI values, the schedule that optimizes synergy will have a Pareto front closest to the origin in the criterion space.

For the A549 cell line, Figure 5a indicates that the "1/2" protocol (pembrolizumab administered QD, bevacizumab Q2D) is optimally synergistic. Once the Pareto optimal schedule is chosen, the next task is dose selection. In Figure 5b, we visualize the Pareto optimal doses for this optimally synergistic schedule. The research team can choose any dose on this front to pursue further, depending on how they want to weigh the CI for SoE, the CI for SoP, the relative TGI, and toxicity and cost concerns. In addition, the team would also need to choose how to define SoP and SoE (here, we used LSD-HSA), as it can be challenging to compare results across criterion spaces. Choosing one space to consider is reasonable when predictions are consistent across the choice of synergy spaces, as was the case here. Here, we chose to use LSD as our SoP metric to avoid classifying combinations with unrealistically high doses of pembrolizumab as optimally synergistic (as is shown to occur in Figure S6 when Loewe is used).

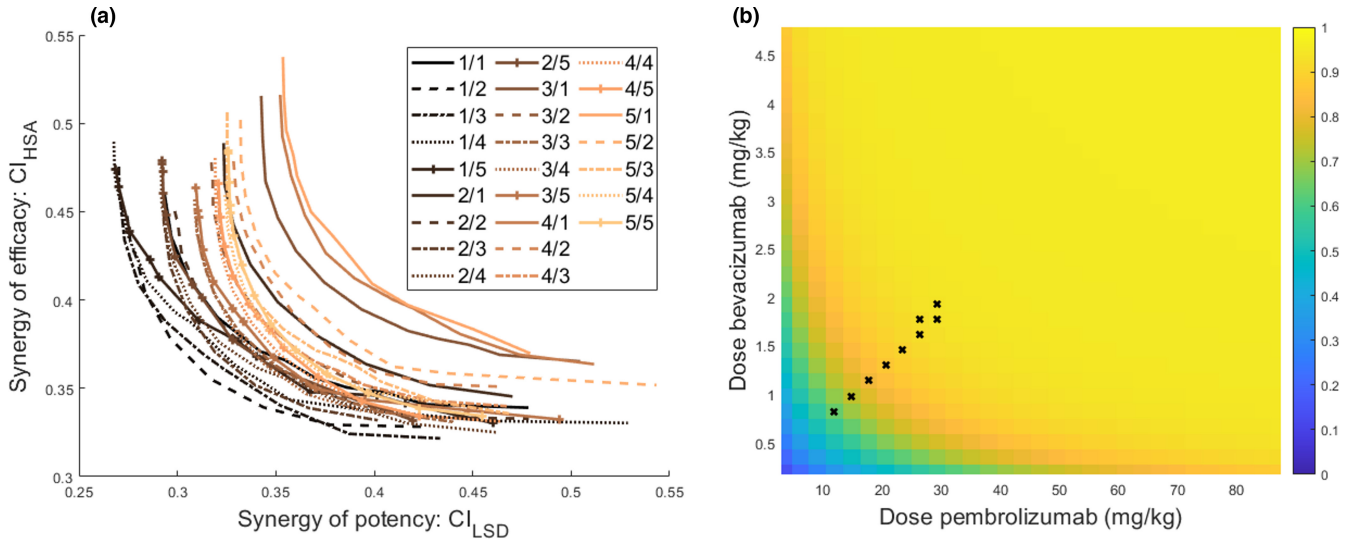


FIGURE 5 (a) A549 Pareto front as a function of protocol for the pembrolizumab and bevacizumab model in LSD-HSA synergy space. Each protocol is indicated in the form m/n where m is the spacing between pembrolizumab doses and n is the spacing between bevacizumab doses. (b) The x indicates doses on the "1/2" Pareto front, which was found to be optimally synergistic for A549 in (a). Color corresponds to the predicted TGI relative to the control for the combination dose administered using the "1/2" protocol. CI, combination index; HSA, highest single agent; LSD, lowest single dose; TGI, tumor growth inhibition.

We chose HSA as our SoE metric as it does not require that drugs elicit their responses independently, which can be difficult to assess.

DISCUSSION

It is widely accepted that the treatment of advanced cancers requires well-designed drug combinations.[24–29] Many have pursued combination design through the lens of drug synergy. However, the large number of synergy metrics available, and their "largely arbitrary" use[3] complicates the process of identifying the most synergistic drugs, and the most synergistic doses for preselected drugs. To address the latter question of identifying synergistically optimal doses, we introduced the MOOCS-DS method, summarized in Figure 6. This approach decouples SoE (using Bliss or HSA) and SoP (using Loewe or the newly proposed LSD framework) through its use of Pareto optimality – that is, by identifying doses for which one synergy metric cannot improve without the other worsening.

We applied MOOCS-DS in two settings. First, we considered a toy model of a logistically growing tumor with two kill terms mimicking the action of two drugs. Second, we considered a novel PK-TGI model describing murine response to the anti-PD-1 checkpoint inhibitor pembrolizumab and the anti-angiogenic agent bevacizumab in two NSCLC lines.[21] Following the MOOCS-DS protocol outlined in Figure 6, we found that the algorithm led us down divergent paths. In the case of the toy model, the combination doses that maximize synergy sensitively depend on the choice of SoP and SoE metrics. We hypothesize that this may occur because the order of magnitude of drug activity are different, with one kill term being linear and the other being quadratic.

When such discrepancies in the synergistically optimal doses emerge, one must proceed with caution in using MOOCS-DS to identify a dose for further experimental consideration. If a research team determines that their drugs meet the assumption of Bliss (dose independence), that would be sound justification for defining SoE using this metric. If the assumption of independence is significantly violated, or that information is simply not available, HSA would be preferred over Bliss as the SoE metric. Similarly, if the drugs satisfy the Dose Equivalence Principle by having near parallel dose response curves, this justifies the choice of Loewe as the preferred SoP metric. If the assumption of parallel curves is significantly violated,

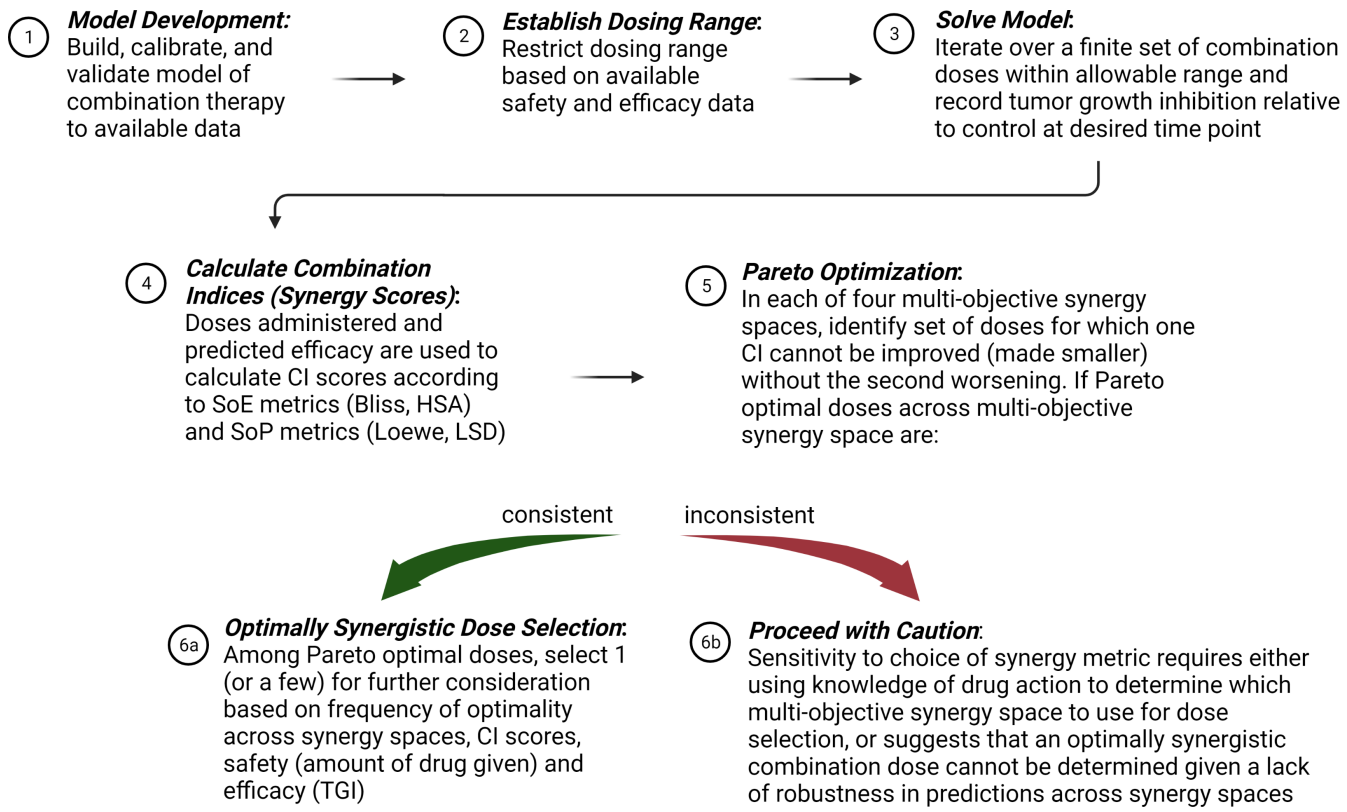


FIGURE 6 Schematic of MOOCS-DS algorithm, including an indication of when the optimal predictions should be interpreted with caution. CI, combination index; HSA, highest single agent; LSD, lowest single dose; MOOCS-DS, Multi-Objective Optimization of Combination Synergy – Dose Selection; SoE, synergy of efficacy; SoP, synergy of potency; TGI, tumor growth inhibition.

LSD would be preferred over Loewe as SoP metric. Thus, although there is a path forward using MOOCS-DS when the various Pareto fronts contain little overlap, one should proceed with caution and understand that the method is going to produce results that sensitively depend on additivity definitions that are challenging to pin down.

In the case of the PK-TGI model of pembrolizumab and bevacizumab, the identified Pareto optimal doses are relatively insensitive to the metric used to define SoE and SoP. This robustness gives us confidence that MOOCS-DS is identifying truly synergistic combination doses. As the method always selects a set of optimal doses, as compared to a single optimal combination dose, the research team still has choices to make in this scenario. In particular, they must weigh the following factors to identify a single combination dose, or a small set of doses, for further experimental study: (1) whether SoE or SoP is more important, (2) in how many of the multi-objective synergy spaces is a combination dose Pareto optimal, (3) what is the TGI associated with the combination, and (4) what is the expected toxicity?

Looking at the Pareto optimal doses identified by MOOCS-DS for the pembrolizumab/bevacizumab model, we found them to be far from the originally tested experimental dose,[21] strongly suggesting that higher preclinical success (and possibly clinical success) could be achieved with a different dosing strategy. We note that, in this analysis, only a single reported combination dose–response curve was available to parametrize the model, and additional tested doses would have provided more confidence in model predictions. Similarly, assessing model sensitivity to parameters prior to implementing MOOCS-DS would help quantify the robustness of the predictions. As an example, one could study how optimally synergistic doses change as a certain parameter value changes over its confidence interval. Alternatively, one could quantify how much variation in an important parameter is permitted if one wants to preserve the Pareto optimal classification of a particular combination dose. Nevertheless, this already demonstrates an exciting approach to model-guided dose selection for combination therapy, where even a single combination dose–response curve can be used to guide dose selection for the next experiment. This can then be used to improve the model's predictive power in an iterative "synergy" between mathematical modeling and experimentation.

The identification of optimally synergistic doses can also inform "go" or "no-go" preclinical decisions. For the p53-deficient H1299 NSCLC cell line, the Pareto optimal solutions give smaller or comparable doses of pembrolizumab than was used in the experiments,[21] whereas for the p53 wild-type A549 NSCLC cell line, the Pareto optimal doses with sufficient TGI require significantly larger pembrolizumab doses than the initially selected experimental dose. This suggests that the combination (using the experimental protocol in ref. 21) may be unfeasible in the p53 wild-type NSCLC (indicating "no-go") but can be applicable in the p53-deficient NSCLC (indicating "go"). Interestingly, MOOCS-DS also determined that the p53 wild-type cells can be changed from a "no-go" to a "go" indication if the spacing of the drugs, and not just the dose, can be altered from the experimental protocol (see Figure 5b). These predictions remain to be verified experimentally.

The combination of pembrolizumab and bevacizumab is already being investigated clinically, with 45 clinical trials listed on clinicaltrials.gov as of October 2022, out of which six are completed and three have posted results. All the trials have tested 200 mg i.v. of pembrolizumab administered Q3W combined with 10 or 15 mg/kg of bevacizumab, given i.v. either Q2W (clinical trial NCT02337491) or Q3W (clinical trial NCT02348008). The results look encouraging for the interventional nonrandomized metastatic renal cell carcinoma trial, which reported that the combination was safe and effective.[30,31] However, in the interventional randomized trial of recurrent glioblastoma (rGBM), the results did not show superiority over monotherapy.[32,33] Interestingly, in a combination nonrandomized recurrent ovarian cancer trial of 200 mg i.v. pembrolizumab and 15 mg/kg bevacizumab given Q3W, the addition of daily oral cyclophosphamide (clinical trial NCT02853318) demonstrated clinical benefit in 95% of patients and durable treatment responses over 12 months in 25% of patients.[34] It would be extremely interesting to assess whether the selected doses and schedules were Pareto optimal, whether a more optimal combination dose exists, and whether lack of success in rGBM could have been predicted preclinically.

Of course, there exist significant translational challenges in using murine experiments to predict efficacy in humans. A primary obstacle is establishing whether this approach can be applied to other biomarkers as a proxy for TGI in animal models, or whether other metrics can be reliably collected and modeled. Notably, standard criteria for assessing disease progression, such as Response Evaluation Criteria in Solid Tumors (RECIST), have been challenged in their applicability, including for translational purposes,[35] and more clinically relevant metrics need to be used. Furthermore, even when appropriate metrics can be collected to establish a quantifiable dose–response relationship, determining the number of data points to collect is highly nontrivial. Model parametrization that is robust to noise and uncertainty generally requires collecting large amounts of data,[36] which can be challenging both technically (i.e., for invasive procedures, such as biopsies), as well as logistically and financially.

In conclusion, the proposed multi-objective synergy optimization approach MOOCS-DS has the potential to support Project Optimus' goal of improving combination therapy design. Because the synergy quantification method is mechanism-agnostic, describing tumor burden reduction solely as a function of drug concentration, it is applicable to a wide range of drugs. Given its versatility, this approach can become an invaluable tool for guiding dose, schedule, and indication selection for combination therapy, including the potential to simply reuse existing drugs in clever ways.

AUTHOR CONTRIBUTIONS

J.L.G. and I.K. wrote the manuscript, designed the research, and analyzed the data. J.L.G. performed the research.

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CONFLICT OF INTEREST STATEMENT

I.K. is an employee of EMD Serono, the US business of Merck KGaA. The research was conducted during J.L.G.'s sabbatical with EMD Serono in the Quantitative Pharmacology Department.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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